

The University of Chicago

THE ADRENALS AND PANCREATIC
DIABETES

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE BIO-
LOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

1936

By

H. WARD FERRILL

Private Edition, Distributed by
THE UNIVERSITY OF CHICAGO LIBRARIES
CHICAGO, ILLINOIS

Reprinted from
ARCHIVES OF INTERNAL MEDICINE
Vol. LX, No. 5, 1937

The University of Chicago

THE ADRENALS AND PANCREATIC
DIABETES

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE BIO-
LOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

1936

By

H. WARD FERRILL

Private Edition, Distributed by
THE UNIVERSITY OF CHICAGO LIBRARIES
CHICAGO, ILLINOIS

Reprinted from
ARCHIVES OF INTERNAL MEDICINE
Vol. LX, No. 5, 1937



Reprinted from the Archives of Internal Medicine
November 1937, Vol. 60, pp. 805-816

Copyright, 1937, by American Medical Association

THE ADRENALS AND EXPERIMENTAL PANCREATIC DIABETES

H. WARD FERRILL

The etiology and course of diabetes mellitus have been associated with adrenal function by various authors since Zuelzer¹ proposed the view that a mutual antagonism exists between the adrenals and the pancreas. He said he believed that the glycosuria which follows pancreatectomy is due to the unchecked diabetogenic action of epinephrine secreted from the adrenals in the absence of the antagonistic action of internal secretion of the pancreas.

More recently the supposed relationship of the adrenals to diabetes and to other diseases has become the basis for surgical intervention or roentgen irradiation of the adrenals in clinical practice. In view of the fact that these procedures involve possible irreparable damage to the indispensable adrenal cortex as well as to the less essential medulla, they should be based on physiologic premises that have indisputable experimental support, or else they should be condemned as too dangerous for life and health to warrant their use as therapeutic measures. We believe that the experimental background for the alleged relation of the adrenals to diabetes is inadequate. Rogoff² has emphasized the possible serious consequences of surgical intervention on the adrenal glands and has reported the development of Addison's disease following an operation on a patient with diabetes.

Some writers have maintained that the medulla is concerned with diabetes; others believe that it is the cortex. Some apparently have considered the adrenal as a single gland, failing to note functional distinction between the indispensable interrenal glandular tissue, or cor-

From the Physiological Laboratory, University of Chicago.

Eli Lilly & Co. supplied the insulin for this and related investigations.

A preliminary report of this work has been published (*Proc. Soc. Exper. Biol. & Med.* **34**:100, 1936).

Aided by the G. N. Stewart Memorial Fund and grants from the Commodore Beaumont Foundation and Mr. Max Manischewitz.

1. Zuelzer, G.: (a) *Experimentelle Untersuchungen über den Diabetes*, Berl. klin. Wchnschr. **44**:474, 1907; (b) *Ueber Versuche einer spezifischen Fermenttherapie des Diabetes*, Ztschr. f. exper. Path. u. Therap. **5**:307, 1908.

2. Rogoff, J. M.: *Addison's Disease Following Adrenal Denervation in a Case of Diabetes Mellitus*, J. A. M. A. **106**:279 (Jan. 25) 1936.

tex, and the chromaffin material, or medulla, of the adrenal body. An extensive literature has accumulated on the alleged rôle of the adrenals in carbohydrate metabolism, much of which fails to indicate whether the supposed influence of the glands is exercised by the cortex or the medulla or both.

Possible relationship of the adrenal medulla to diabetes can be studied more easily than that of the adrenal cortex. The output of epinephrine can be measured, and the rate of secretion of epinephrine in normal animals under ordinary experimental conditions is known.³

Liberation of epinephrine can be suppressed without serious consequences in otherwise normal animals.⁴ If secretion of epinephrine plays a significant rôle in experimental pancreatic diabetes, its suppression should affect the development or course of diabetes in depancreatized animals. We have made experimental studies to determine whether this occurs and also quantitative as well as qualitative studies of secretion of epinephrine in relation to experimental pancreatic diabetes.

In previous communications⁵ it was reported that unilateral adrenalectomy or interference with secretion of epinephrine (by adrenal denervation and other procedures) ameliorated diabetes in depancreatized dogs, that in animals previously rendered diabetic (by pancreatectomy) the adrenal operation diminished the glycosuria and that in dogs previously subjected to the adrenal operation pancreatectomy failed to cause or caused only a mild degree of glycosuria. The amount of insulin required (on a constant diet) for controlling the glycosuria was reported to be decidedly less as the result of the adrenal operations, which were said also to render the animals more sensitive to insulin. These statements are in agreement with conclusions reported by others.

3. Stewart, G. N., and Rogoff, J. M.: The Average Epinephrin Output in Cats and Dogs, *Am. J. Physiol.* **66**:235, 1923.

4. Stewart, G. N., and Rogoff, J. M.: (a) Quantitative Experiments on the Liberation of Epinephrin from the Adrenals After Section of Their Nerves, with Special Reference to the Question Whether Epinephrine Is Indispensable for the Organism, *J. Pharmacol. & Exper. Therap.* **10**:1, 1917; (b) Further Observations Showing that Epinephrine from the Adrenals Is not Indispensable, *Am. J. Physiol.* **48**:397, 1919.

5. (a) Barnes, B. O.; Scott, V. B.; Ferrill, H. Ward, and Rogoff, J. M.: Effects of Partial Adrenalectomy on Experimental Diabetes and on Sensitivity to Insulin, *Proc. Soc. Exper. Biol. & Med.* **31**:524, 1934; (b) The Effects of Partial and Complete Adrenalectomy on Experimental Diabetes, *Am. J. Physiol.* **109**:35, 1934; Further Studies on the Effects of Partial Adrenalectomy on Experimental Diabetes, *ibid.* **109**:89, 1934; The Sensitivity to Insulin, *ibid.* **109**:95, 1934. (c) Ferrill, H. Ward; Rogoff, J. M., and Barnes, B. O.: Further Studies on the Influence of the Adrenal Glands on Experimental Diabetes, *ibid.* **113**:41, 1935.

On further examination of the experimental data and in view of satisfactory control experiments, we found it necessary to revise the foregoing interpretations. Under more suitable conditions, we have repeated the experiments and have made more extensive quantitative studies of the output of epinephrine from the adrenals of experimental animals and of an adequate series of control depancreatized dogs. In the former series, in which there were about 40 animals, the postoperative and other experimental conditions were not as satisfactorily controlled as in the present series of experiments. One of the animals (on the history of which was based the statement that little or no diabetes follows pancreatectomy if the adrenals are interfered with) was found at autopsy to possess a substantial portion of pancreas, and in one or two others a number of nodes were observed along the duodenum and were preserved for histologic examination. With improved conditions of experimental procedure and suitable controls, it became obvious that we had been misled in the evaluation of the previous experimental data.

The present report is concerned chiefly with experiments to determine whether reduction or suppression of secretion of epinephrine from the adrenal glands exerts a significant influence on experimental pancreatic diabetes.

In these, as in the earlier experiments, the criterion was the amount of insulin required to maintain the level of sugar excreted in the urine below about 5 Gm. daily and the concentration of sugar in the urine under about 1 per cent. The experiments were performed on dogs. All the experimental and control animals were kept under identical or comparable conditions and on a constant diet, consisting of 500 Gm. of boiled beef lung and 100 Gm. of sucrose daily, divided into two meals. To the morning meal was added 50 Gm. of fresh raw beef pancreas. Drinking water was available at all times. The amount of insulin for each day was divided into two doses and given at the time of feeding. Urine was collected for twenty-four hours; the quantity excreted and the sugar content were determined at the same hour each morning.

Interference with secretion of epinephrine was accomplished by excision of one adrenal gland and denervation of the other gland. In addition to denervation, the medulla of the remaining gland was curetted by drilling with a dental burr so that most of the medulla was destroyed or damaged. For these animals the adrenal operations were performed in two stages, and pancreatectomy was performed during the interval between the adrenal operations. Other dogs were depancreatized without the subjection of the adrenals to operations for reducing the secretion of epinephrine. These served as controls. At the end of different periods of observation the experiments were terminated, so that quantitative determination of the degree of reduction or suppression of secretion of epinephrine could be made (by the method employed by Stewart and Rogoff).

Twenty-one animals were studied in this series of experiments. In these, as well as in some of the better experiments of the previous

group, after a few weeks of observation the animals usually showed a reduction in the amount of insulin required to maintain glycosuria at the low level. This cannot be attributed to loss of weight, since the animals of the present series lost little if any weight, although most of the former animals were in much poorer condition. It might appear that in depancreatized animals subjected to interference with secretion of epinephrine from the adrenals the reduced requirement for insulin is due to reduced secretion of epinephrine. However, this cannot be the case, since the requirement for insulin does not decline until several weeks after pancreatic diabetes has been induced. Indeed, it appears at a time when regeneration of nerves might occur in the animals after adrenal denervation and when secretion of epinephrine might be expected to have become reestablished. In any case, the reduction of the amount of insulin required cannot be attributed to the operation for suppression of secretion of epinephrine, since it occurs in control depancreatized dogs not subjected to adrenal operations but otherwise under the same conditions as the experimental animals.

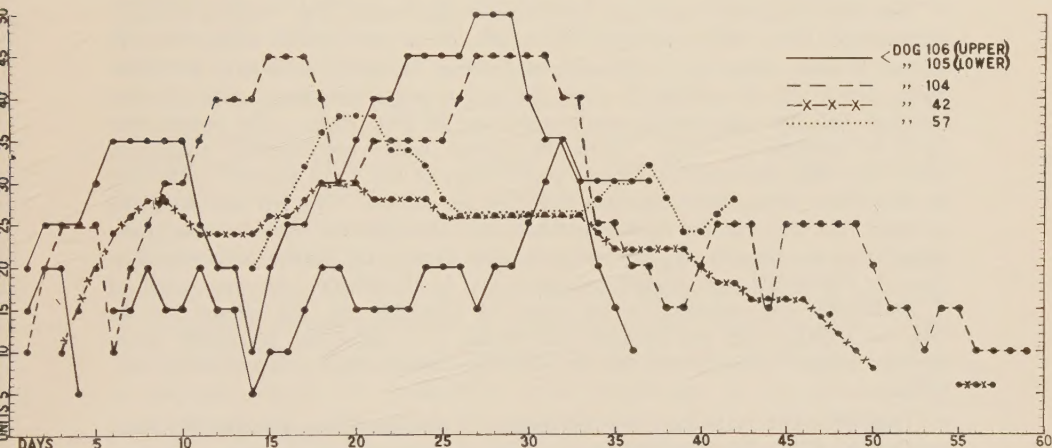
We have observed the decline in requirement for insulin in experimental animals with reduced or suppressed secretion of epinephrine and in some with the ordinary normal rate of secretion (indicating either inadequate denervation or regeneration of adrenal nerves). It is obvious that the requirement for insulin is not modified by the functional state of the adrenal medulla. The range of dosage of insulin required over a period of weeks or months is similar in control depancreatized dogs and in those with a reduced or suppressed output of epinephrine. We have found a high or low requirement for insulin associated with a low or normal output of epinephrine. This may be seen in different animals or in one animal at different times, regardless of whether or not, in addition to pancreatectomy, secretion of epinephrine has been suppressed.

The most significant observation that we have made is that in control depancreatized dogs (not subjected to interference with the adrenals), kept under the same conditions as the other experimental animals, sooner or later the output of epinephrine from the adrenals may become markedly reduced or suppressed. This phenomenon and the possible mechanism responsible for it are still under investigation and will be the subject of another report.

The accompanying chart illustrates the general results obtained. One record (dog 42), the best for the former experiments, is included because the interval between the adrenal operations and pancreatectomy was much longer than that in the later experiments; the rest are for the present series. Each record represents a typical experiment, illus-

trating the various results obtained for different groups of the series. Two dogs (42 and 57) were subjected to operations for suppression of secretion of epinephrine in addition to pancreatectomy; the other three were only depancreatized. These five experiments will be described in the following condensed protocols:

Dog 42.—Both adrenals of this female dog were denervated, and the medulla was drilled, the left on July 13 and the right on July 21, 1934. On Jan. 2, 1935, pancreatectomy was performed. During the ensuing five weeks the requirement for insulin ranged between 24 and 30 units daily; then it declined during the next three weeks to 6 units daily. On March 1 (fifty-eight days after pancreatectomy) the animal (weight, 6.05 Kg.) was killed and the output of epinephrine from the adrenals was determined. With the animal under pentobarbital anesthesia blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 1.53 Gm. per minute. The concentration of



The requirement for insulin, with a daily diet of 500 Gm. of boiled beef lung, 100 Gm. of cane sugar and 50 Gm. of raw beef pancreas, after pancreatectomy with and without suppression of secretion of epinephrine from the adrenal glands of dogs.

epinephrine was estimated, a segment of rabbit intestine being used. The epinephrine concentration in the blood from the adrenal vein was much less than 1:30,000,000 and somewhat less than 1:50,000,000, which was the limit of sensitivity for the segment. If the blood from the adrenal vein contained this concentration, it would correspond to 0.00003 mg. per minute for the dog or 0.000005 mg. per kilogram per minute, i. e., about one fiftieth of the average output for normal animals, as determined by Stewart and Rogoff³ (1923). There probably was not more than one seventy fifth to one one hundredth of the average output of epinephrine for normal dogs under ordinary experimental conditions.

Dog 57.—On April 6, 1935, the right adrenal was removed from this male dog (weight 13.5 Kg.). On April 26 pancreatectomy was performed, the animal weighing 13.7 Kg. On May 9, when the weight was 11.6 Kg., the left adrenal was denervated, and the medulla was drilled. From April 30 to May 3, inclusive, the

dosage of insulin was doubled by mistake (insulin containing 40 units instead of 20 per cubic centimeter being used), reaching 70 or 80 units daily, without ill effect. Thereafter, the requirement for insulin ranged between 24 and 38 units daily. On June 8, forty-three days after pancreatectomy (weight, 11.2 Kg.), the requirement for insulin was 28 units (ascending), and the sugar content of the blood (a. m.) was 320 mg. per hundred cubic centimeters. The animal was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 2.7 Gm. per minute. The remaining adrenal gland (left) weighed 0.57 Gm.; it had undergone fibrosis, and the upper half was sclerotic. The concentration of epinephrine in the blood from the adrenal vein was much less than 1:50,000,000 and not as great as 1:75,000,000. If the blood contained 1:75,000,000 epinephrine, the output would correspond to 0.000035 mg. per minute for the dog, or 0.0000031 mg. per kilogram per minute; i. e., the output of epinephrine was less than one seventy fifth of the average output for normal animals under ordinary experimental conditions.

Dog 104.—Pancreatectomy was performed on this female dog (weight, 8.8 Kg.) on Sept. 26, 1935. The requirement for insulin for about a month ranged between 25 and 40 units daily; then it fell, ranging between 15 and 25 units daily for about three weeks. On November 25 (sixty days after pancreatectomy), when the dog weighed 7.65 Kg., the insulin requirement was 10 units daily. The animal was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 8.67 Gm. per minute. The left adrenal gland weighed 0.64 Gm. and the right gland 0.70 Gm. Epinephrine concentration in the blood from the adrenal vein was distinctly less than 1:125,000,000, somewhat less than 1:250,000,000 and slightly greater than 1:375,000,000. It was taken at 1:300,000,000, corresponding to an output of 0.0000286 mg. per minute for the dog, or 0.0000037 mg. per kilogram per minute, i. e., about one seventieth of the average output of epinephrine for normal dogs under ordinary experimental conditions.

Dog 105.—Pancreatectomy was performed on this male dog (weight, 8.5 Kg.) on Oct. 26, 1935. The requirement for insulin during most of the entire period of observation ranged between 15 and 20 units daily. On Dec. 2 (thirty-seven days after pancreatectomy), when the dog weighed 7.4 Kg. and the requirement for insulin was 10 units, it was used for epinephrine assay. With the animal under pentobarbital anesthesia blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 4.95 Gm. per minute. The left adrenal gland weighed 0.47 Gm. and the right one 0.5 Gm. Epinephrine concentration in the blood of the adrenal vein was greater than 1:12,000,000, somewhat greater than 1:6,250,000 and less than 1:3,750,000. The reaction on the segment of intestine was not unlike that of 1:5,000,000. It was taken at 1:5,000,000, corresponding to an output of epinephrine of 0.001 mg. per minute for the dog, or 0.000135 mg. per kilogram per minute, i. e., within the usual range for normal dogs under ordinary experimental conditions.

Dog 106.—Pancreatectomy was performed on this female dog (weight 9.5 Kg.) on Oct. 26, 1935. The requirement for insulin rose to 50 units daily during about a month and then declined to 30 units daily for the last five days of observation. On December 3 (thirty-eight days after pancreatectomy), when the animal weighed 8.5 Kg. and the requirement for insulin was 30 units daily, it was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was

obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 4.25 Gm. per minute. The adrenal glands weighed 0.56 Gm. each. Epinephrine concentration in the blood from the adrenal vein was decidedly greater than 1:5,000,000, somewhat greater than 1:3,750,000, less than 1:2,500,000 and not far from 1:3,125,000. It was taken at 1:3,000,000, corresponding to an output of epinephrine of 0.0014 mg. per minute for the dog, or 0.00017 mg. per kilogram per minute, i. e., within the usual range for normal dogs under ordinary experimental conditions.

For three animals (dogs 56, 57 and 60) the dose of insulin was doubled by mistake. A supply of insulin containing 40 units per cubic centimeter was used, whereas previously the insulin contained 20 units per cubic centimeter. For four days, instead of the intended 35 to 40 units daily, the animals received 70 to 80 units daily before the error was discovered. In two instances one adrenal gland had been excised and pancreatectomy performed; in the third case one adrenal gland was denervated before pancreatectomy. No ill effects were observed from these enormous doses of insulin. We must conclude, therefore, that in depancreatized animals the supposed increase in sensitivity to insulin reported to occur after unilateral adrenalectomy or adrenal denervation is without foundation. A number of animals that had only been depancreatized were killed at intervals of about one to eight weeks after removal of the pancreas. The output of epinephrine was determined for these to observe how soon reduction might be detected. In some the requirement for insulin at the time was relatively high; in others it was low. A reduction in the secretion of epinephrine was found as early as ten and eleven days after pancreatectomy in some animals, while in others a normal output of epinephrine was found five or six weeks after pancreatectomy. We found no relation between the requirement for insulin and the rate of secretion of epinephrine in the animals studied.

COMMENT

The literature on the adrenal glands in relation to carbohydrate metabolism is too extensive for us to attempt more than a review of a few papers that have a more or less direct bearing on the particular phase of the subject under consideration. The earlier papers are concerned chiefly with the question of relationship of the adrenal medulla, although some of them do not make clear whether a relationship of the medulla or of the cortex is supposed to exist. In the more recent literature can be found support for either view, i. e., that the cortex plays an important or indispensable rôle in carbohydrate metabolism or that the medulla plays such a rôle.

Studies of the influence of administration of epinephrine on carbohydrate metabolism may be viewed as being mainly of pharmacologic interest. Few investigations of this nature can have physiologic sig-

nificance, since the dosage of epinephrine is usually much in excess of the amounts known to be within the physiologic range of secretion. Often the epinephrine is administered subcutaneously. Owing to the local vasoconstrictor action of epinephrine absorption is rarely at a uniform rate, indeed, differences in physiologic action have been reported between the subcutaneous and the intravenous administration of the same quantities of epinephrine.

Of those who have supported the view that the cortex is directly concerned in an important manner with carbohydrate metabolism, none can be said to have produced adequate experimental proof. Britton and Silvette⁶ have maintained that the adrenal cortex exercises a "prepotent function" on carbohydrate metabolism and that in adrenalectomized animals the effect on carbohydrate metabolism "appears to be primarily responsible for death." Rogoff and Stewart⁷ have shown that moderate hypoglycemia occurs in adrenalectomized animals when acute symptoms of cortical insufficiency develop. However, some animals may manifest important symptoms of insufficiency and show no significant decline in the sugar content of the blood. This is true, also, for human beings with Addison's disease. The view held by Britton and Silvette that severe hypoglycemia, "commonly to the convulsive level," occurring in animals "as early as 18 to 48 hours after operation," accounts for death of adrenalectomized animals is not tenable in the light of the experimental work of others. The results indicated that their adrenalectomized animals were not in as good condition as they should have been from eighteen to forty-eight hours after operation.

Hartman and Brownell⁸ reported studies on nine cats and concluded that their results indicated that "cortin is essential for the maintenance of diabetes." Although they administered an extract of adrenal cortex, most of their adrenalectomized animals did not survive as long as untreated adrenalectomized cats usually do.⁹ Of course these were also depancreatized. Nevertheless, the conclusions need not be accepted merely because this additional handicap existed. The experiments would be of value only if the depancreatized and adrenalectomized animals

6. Britton, S. W., and Silvette, H.: The Apparent Prepotent Function of the Adrenal Glands, *Am. J. Physiol.* **100**:701, 1932.

7. Rogoff, J. M., and Stewart, G. N.: Studies on Adrenal Insufficiency in Dogs: II. Blood Studies in Control Animals Not Subjected to Any Treatment, *Am. J. Physiol.* **78**:711, 1926.

8. Hartman, F. A., and Brownell, K. A.: Relation of Adrenals to Diabetes, *Proc. Soc. Exper. Biol. & Med.* **31**:834, 1934.

9. Rogoff, J. M., and Stewart, G. N.: (a) Studies on Adrenal Insufficiency: VIII. The Survival Period of Untreated Adrenalectomized Cats, *Am. J. Physiol.* **88**:162, 1929; (b) Studies on Adrenal Insufficiency: IX. The Influence of Extracts of Adrenal Cortex (Sheep and Cattle) on the Survival Period of Adrenalectomized Dogs and Cats, *ibid.* **91**:254, 1929.

were in sufficiently good condition to permit studies that were not complicated by serious postoperative conditions. Indeed, the only cat that survived long enough to permit satisfactory studies showed a condition exactly opposite to that mentioned in their conclusion. The animal survived thirty-eight days after bilateral adrenalectomy. "For three weeks or more during this latter period there was no reduction in diabetes but after this time there was marked reduction which large amounts of cortin failed to restore." Adrenal cortex extract prepared by Hartman's salt precipitation method has been proved to be incapable of prolonging life in adrenalectomized animals.^{9b} Since then he has employed extracts of adrenal cortex prepared by a different process. It may be pointed out that since Hartman¹⁰ has maintained that the adrenal cortex produces epinephrine, he could not be certain that any effect attributed to action of his extract might not have been due to presence of epinephrine or related principles.

From the pharmacologic antagonism existing between epinephrine and insulin it seems that the alleged relation of the adrenal medulla to pancreatic diabetes rests on a more substantial basis. However, the evidence afforded by properly controlled experimental work and by adequate quantitative studies does not show such a relationship. Older literature on this question has been reviewed in a number of papers by Stewart and Rogoff¹¹ on carbohydrate metabolism, particularly in the paper entitled "The Adrenals and Pancreatic Diabetes."¹² In that paper it was shown that diabetes develops in depancreatized animals in the absence of secretion of epinephrine to the same degree as in those without interference with the adrenals. After total ablation of the adrenals pancreatic diabetes continues to exist if the postoperative consequences of adrenalectomy are not too severe. If adrenalectomy is followed by a rapid decline of the animal and short survival or if after a period of good postoperative recovery acute insufficiency of adrenal cortex supervenes, the sugar content of the blood may fall to or below the normal level, and glycosuria may become considerably diminished.

10. Hartman, F. A., and Hartman, W. B.: The Production of Epinephrin by the Adrenal Cortex, *Am. J. Physiol.* **65**:623, 1923.

11. Stewart, G. N., and Rogoff, J. M.: The Alleged Relation of the Epinephrin Secretion of the Adrenals to Certain Experimental Hyperglycemias, *Am. J. Physiol.* **44**:543, 1917; The Relation of the Adrenals to Piqure Hyperglycemia and to the Glycogen Content of the Liver, *ibid.* **46**:90, 1918; Further Observations on the Relation of the Adrenals to Certain Experimental Hyperglycemias (Ether and Asphyxia), *ibid.* **51**:366, 1920; The Action of Insulin on Adrenalectomized Rabbits, *ibid.* **65**:342, 1923.

12. Stewart, G. N., and Rogoff, J. M.: The Adrenals and Pancreatic Diabetes, *Am. J. Physiol.* **65**:319, 1923.

Turcatti¹³ concluded that combined pancreatectomy and adrenalectomy interfere with the development or reduce the severity of pancreatic diabetes. This did not occur if, instead of adrenalectomy, the glands were denervated. He admitted that his conclusions cannot be considered categorical, since the animals survived for too short a time. None of his fourteen experimental animals survived beyond forty hours. All succumbed within from eight to forty hours.

Carrasco Formiguera and Puche¹⁴ concluded that denervation of the adrenals does not influence pancreatic diabetes. Their experiments were made on two dogs, in one complete and in the other partial pancreatectomy having been performed. Ciminata¹⁵ has supported the view that diabetes in human beings can be successfully treated by denervation of the adrenal glands. This is based on his experiment performed in 1928 on one dog in which he obtained a rapid decrease in the sugar content of the blood and in glycosuria after bilateral denervation of the adrenals.

Cannon, McIver and Bliss¹⁶ obtained an increase in rate of the denervated heart after administration of insulin, when the sugar content of the blood fell to between 70 and 80 mg. per hundred cubic centimeters in cats anesthetized with a compound of chloral and dextrose. This increase in heart rate was interpreted as indicating liberation of epinephrine from the adrenals to counteract the insulin hypoglycemia. The effect was not obtained if the adrenals were excised or denervated. It is now evident that the "denervated" heart is not a reliable indicator for quantitative studies on the secretion of epinephrine from the adrenals. Cannon, Lewis and Britton¹⁷ have shown that the so-called denervated heart (as employed by Cannon, McIver and Bliss) may not be entirely denervated, since they found "evidence for accessory accelerator fibers from the thoracic sympathetic chain." Other evidence from the same laboratory shows that the cardio-acceleration may be obtained by influence of the thyroid and of the liver, as well as of the

13. Turcatti, E.: Surrénale et diabète pancréatique, *Compt. rend. Soc. de biol.* **102**:466 (Nov. 8) 1929.

14. Carrasco Formiguera, R., and Puche, J.: Enervation des surrénales et diabète expérimental, *Compt. rend. Soc. de biol.* **108**:171 (Oct. 12) 1931.

15. Ciminata, A.: Influence of Division of Nerves of Suprarenals on Diabetes Mellitus, *Klin. Wchnschr.* **11**:150 (Jan. 23) 1932; abstr., *J. A. M. A.* **98**:1421 (April 16) 1932.

16. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XIII. Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, *Am. J. Physiol.* **69**:46, 1924.

17. Cannon, W. B.; Lewis, J. T., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XVII. A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, with Evidence for Accessory Accelerator Fibers from the Thoracic Sympathetic Chain, *Am. J. Physiol.* **77**:326, 1926.

adrenal. Finally, the acceleration can be obtained even in the absence of the adrenals or of the influence of the thyroid or liver. It has been accounted for by Cannon and his collaborators as due to a sympathomimetic hormone, which they called sympathin. The reaction relied on by Cannon, McIver and Bliss therefore could not yield reliable quantitative information on adrenal secretion of epinephrine.

Whether or not insulin is capable of influencing secretion of epinephrine has not been satisfactorily determined. Statements can be found in the literature indicating that insulin is without effect and others that it may affect secretion of epinephrine in either direction. Methods of investigation on which these statements are based are not sufficiently reliable. In our own experience, by collecting blood from the adrenal vein by way of the "cava pocket" and utilizing rabbit intestine for determining the concentration of epinephrine in the blood, we have failed thus far to find any significant alteration in the rate of secretion of epinephrine from the adrenals after administration of insulin under the conditions of our experiments. This question is still under investigation.

We believe that the experiments reported in this paper are adequate to show that the alleged relation between the adrenal medulla and pancreatic diabetes does not exist. As in the experiments of others, when we made observations on animals that were in poor condition, we also found milder diabetes. This we interpret as indicating that the condition of the animal was too poor to enable it to react by the development of glycosuria of the same intensity as may occur in depancreatized animals in good condition. For the animals that withstood the experimental conditions better and were obviously in a much more satisfactory physical state, our experiments clearly showed that pancreatic diabetes is not modified by a reducing or suppressing of secretion of epinephrine from the adrenals. On the other hand, we have obtained evidence that the diabetic state, under the conditions of our experiments, may lead to interference with liberation of epinephrine from the adrenals. We believe, therefore, that the supposed relation of the adrenal medulla to diabetes as a basis for the clinical practice of intervention with the adrenal glands does not have the support of unequivocal experimental evidence.

CONCLUSIONS

The supposed dependence of experimental pancreatic diabetes on secretion of epinephrine from the adrenals is not supported by substantial experimental evidence.

Severity of diabetes in depancreatized dogs is not modified by reduction or suppression of secretion of epinephrine from the adrenals.

The requirement for insulin, when the diet is constant, is within the same range in depancreatized dogs as in dogs with a reduced or suppressed secretion of epinephrine in addition to pancreatectomy.

Depancreatized dogs with a reduced or suppressed secretion of epinephrine are not more sensitive to insulin than ordinary depancreatized dogs.

Depancreatized dogs kept for several weeks on a constant diet with adequate amounts of insulin to control glycosuria sooner or later show a reduction or suppression of output of epinephrine from the adrenals.

Results obtained for depancreatized animals that have been subjected to operations on the adrenals should be interpreted with caution unless the animals are obviously in excellent physical condition.

The clinical practice of intervention with the adrenal glands for the relief of diabetes (or other conditions, except unilateral malignant neoplasm) does not rest on unequivocal experimental premises, and it should be deprecated as too dangerous for life and health.

